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EDITORIAL COMMENT

Is a Drug-Eluting Stent the Default Treatment Strategy for Drug-Eluting Stent Restenosis?*

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In 2001, when Morice et al. (1) presented the initial results of RAVEL (The Randomized Study With the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions), showing 0% angiographic restenosis 6 months after implantation of a sirolimus-eluting stent, very few people would have envisaged that more than 10 years later, there would be a need for a trial to evaluate the best treatment strategy for drug-eluting stent (DES) in-stent restenosis (ISR).

Although widespread use of DES (versus bare-metal stents [BMS]), advances in stent design, and greater operator experience have all significantly reduced the incidence of restenosis and resultant target vessel revascularization (2), a low rate of ISR continues to exist and it is not benign. Outcomes are even poorer for those with DES compared with individuals presenting with BMS-ISR (3).

There are several treatment options for DES-ISR (e.g., repeat percutaneous coronary intervention, plain old balloon angioplasty, cutting balloons, and drug-eluting balloon [DEB] treatment). Current evidence supports the use of a paclitaxel DEB, which has been shown to be superior for the treatment of both BMS-ISR and DES-ISR compared with the use of plain old balloon angioplasty. An alternative approach for DES-ISR is another DES, with the first-generation paclitaxel DES demonstrating similar efficacy to a paclitaxel DEB (4,5). However, there is a paucity of data examining the role of second-generation DES, and long-term outcome data beyond 1 year are completely lacking.

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In this issue of the *Journal*, 2 important studies address the optimal treatment of DES-ISR. Alfonso et al. (6) report the results of the prospective, multicenter, open-label, randomized RIBS IV (Restenosis Intra-Stent: Drug-Eluting Balloon vs. Everolimus-Eluting Stent) study. The investigators evaluated the role of second-generation everolimus-eluting stents (EES) versus paclitaxel DEB for the treatment of DES-ISR. Also, Habara et al. (7) report the findings of a retrospective single-center investigation of consecutive patients presenting with ISR treated with paclitaxel DEB addressing early and late angiographic findings with clinical follow-up.

There are several important factors to consider before interpreting the results of these studies. Patients presenting with DES-ISR have already failed the best currently available antirestenosis treatment; thus, the challenge of achieving an acceptable long-term result is more difficult. Whereas mechanical factors (e.g. stent underexpansion, stent fracture) or technical factors (e.g. residual uncovered atherosclerotic plaque) may account for some instances of DES-ISR, the most important potential mechanism is tissue hyperplasia with resistance to antiproliferative drugs or hypersensitivity to the stent (8). The large volume of hyperplastic tissue represents a baseline problem for any technology relying solely on balloon dilation. Treatment with DEB is therefore unlikely to achieve acute luminal gain to

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the same extent as another stent that can compress this tissue.

Despite these limitations, the impetus to evaluate the efficacy of DEB treatment for DES-ISR is driven by the concern of the negative long-term effects on the coronary vessel associated with multiple metal layers (9). Furthermore, DEB use may be more favorable in certain patients who cannot continue long-term dual antiplatelet therapy or those already presenting with multiple stent layers as a consequence of recurrent resistant DES-ISR.

In RIBS IV (6), 309 patients presenting with DES-ISR were randomized to treatment with DEB (n = 154) or EES (n = 155). There were no significant differences between groups in regard to baseline clinical or procedural characteristics. Importantly, lesions included were not of high complexity and those at greatest risk of recurrence (lesions >30 mm, in-stent total occlusion) were excluded. The investigators highlighted their careful attention to lesion preparation to ensure no adjacent vessel damage or geographical miss, with liberal use of adjunctive intravascular imaging if indicated, all of which contributed to a 100% angiographic success rate. Both treatment strategies appeared to be technically feasible with a low crossover rate (5 patients in the DEB group, 1 patient in the DES group). In this context, DEB use was favorable with a late loss of around 0.30 mm, similar to that reported in the ISAR-DESIRE 3 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis: 3) study (4). In comparison, treatment with EES resulted in a late loss of 0.18 mm, which, when considered in the setting of higher acute gain, resulted in a larger vessel lumen at follow-up.

In-segment luminal diameter, the primary endpoint evaluated in 90% of all eligible patients at follow-up (median interval: 247 days), was significantly greater in the EES group (2.03 ± 0.7 vs. 1.80 ± 0.6; p < 0.01) and appeared to be true across numerous pre-specified variables (although the study was not powered for subgroup analysis). Other angiographic findings including net gain, loss index, and late loss also appeared to favor EES treatment. Differences in clinical events in the first year favored EES and were driven by target lesion revascularization (TLR) (19 in the DEB group and 6 in the EES group), with no differences in definite stent thrombosis, myocardial infarction, cardiac death, and all-cause mortality.

The study by Habara et al. (7) reports long-term results after treatment of consecutive patients presenting to a single center with ISR and treated with a paclitaxel DEB. Of the 468 patients (550 ISR lesions) treated, the majority (436 lesions) were for DES-ISR with the remaining 114 lesions for BMS-ISR. In addition to clinical follow-up, the patients underwent early (6 to 12 months, 89% of lesions) and late (12 to 24 months, 88% of lesions) angiographic follow-up.

Pre-dilation was performed before DEB treatment for all lesions, and balloon length was chosen to cover the lesion by at least 2 mm at both the proximal and distal margins. Keeping with current guidelines, the recommended inflation time was 60 seconds. Binary restenosis was defined as stenosis occupying >50% of the lumen of the vessel and late restenosis was defined as diameter stenosis ≥50% in lesions that had <50% diameter stenosis at early follow-up.

At early angiographic follow-up, recurrent restenosis occurred in 13 lesions (13%) in the BMS-ISR group and in 82 lesions (21.1%) in the DES-ISR group. This resulted in TLR being performed in 7 lesions (7%) in the BMS group and 54 lesions (13.9%) in the DES-ISR group (p = 0.002), which supports previous studies suggesting better efficacy of DEB treatment in BMS-ISR lesions (10,11) compared with efficacy of DES-ISR treatment (12).

The most notable finding, however, was a "second wave" of late loss in DES-ISR lesions when assessed by late angiographic follow-up. Late restenosis was significantly greater in the DES-ISR group (50 lesions, 16.8%) compared with 2 lesions (2.5%) in the BMS-ISR group (p < 0.001). Delayed late loss was also significantly greater in the DES-ISR group (0.09 ± 0.29 mm vs. 0.22 ± 0.50 mm; p = 0.004) and did not appear to be related to the type of DES initially implanted, with 70% of original lesions treated with a first-generation DES and 30% with a second-generation DES (binary restenosis: 21.8% vs. 19.5%; p = 0.61; TLR: 14.9% vs. 11.5%; p = 0.38; late lumen loss: 0.32 ± 0.23 mm vs. 0.23 ± 0.53 mm; p = 0.12). These angiographic findings translated to a significant difference in TLR at 24 months (8.7% BMS-ISR vs. 24.2% DES-ISR; log rank p = 0.003). There were no differences between groups with regard to the composite endpoints of cardiac death, myocardial infarction, or target lesion thrombosis at 24 months (log rank p = 0.8).

Have the results of these 2 important studies marginalized the role of DEB for the treatment of DES-ISR? We still lack a definitive answer. Advocates of DEB treatment may state that better lesion preparation with a cutting or scoring balloon may have resulted in better acute gain. Furthermore, all currently available DEB are coated with paclitaxel due to its lipophilic properties. However, paclitaxel has now been superseded by sirolimus (and its analogues)

in the setting of DES as the antiproliferative drug of choice due to its superiority (13). By virtue of its pharmacology, the ability to deliver adequate sirolimus drug doses to the vessel wall with current balloon delivery systems has hampered its use. Novel drug delivery technologies in development may enable production of sirolimus-eluting balloons (14). Therefore, the proven superior antiproliferative action of limus compounds versus paclitaxel demonstrated with metal stents (13) also may be true with DEB treatment. Finally, longer-term angiographic and clinical follow-up data are required before definitively concluding that EES is superior to DEB for DES-ISR.

Another approach that should be considered for the treatment of DES-ISR is the use of bioresorbable scaffolds, which theoretically would achieve excellent acute gain without the potential long-term consequences of an additional metal layer in the vessel wall. However, the advantages (e.g., positive remodeling) associated with scaffold use would be nullified by the presence of the previous metal stent.

Currently, we can conclude that the use of EES for DES-ISR is safe and effective but the role of DEB in this context is limited. However, unanswered questions remain. Is it possible to identify some DES-ISR lesions where DEB treatment would be equivalent or superior to EES? Will a new limus DEB be better than current paclitaxel DEB for the treatment of DES-ISR and therefore challenge the results of RIBS IV? While awaiting new data, the strategy of stenting a stent, even if not perceived as particularly elegant, should be the default approach for most lesions presenting with DES restenosis.

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